REMARKS

This Amendment responds to the Office Action mailed May 29, 2009. With this amendment, Applicants amend claims 3 and 5. Applicants note that the Office has deemed claims 4, 10-11, and 13-32 as being directed to non-elected subject matter and withdrawn from consideration. Applicants note that claims 1, 2, and 12 have been canceled previously. No new matter is added with the present amendment. Support for the amendment can be found throughout the specification and claims as filed, including, e.g., in paragraph [0063]. Claims 3 and 5-9 are pending and under consideration with this amendment.

Formalities

Applicants note with appreciation that the Office has withdrawn prior rejections of the claims under 35 U.S.C. § 112, first and second paragraph.

Claim Rejections – 35 U.S.C. § 112, First Paragraph – Enablement

The Action rejects claims 3, 5-9, and 12, under 35 U.S.C. § 112, first paragraph, as allegedly failing to satisfy the enablement requirement. In particular, the Action asserts that while the specification does enable "a method of determining myocardial infarction in a human comprising detecting a homozygous A allele at the nucleotide 80 of SEQ ID No. 3 wherein a homozygous A allele is indicative of myocardial infarction," the specification "does not reasonably provide enablement for determining any arteriosclerotic disease in humans" (Office Action, page 3).

Applicants respectfully note that, without expressing agreement with or acquiescence to the rejection, claims 3 and 5 have been amended, and are now drawn to, at least, "[a] method for determining an increased risk of an arteriosclerotic disease in humans." Applicants note that claims 6-9 depend directly or indirectly from the amended claims, and therefore, benefit from the amendments. These amendments find support in the specification, at for example, page 13.

With respect to the language of the rejection, Applicants note that when the Office states that the specification "does not reasonably provide enablement for determining *any*

arteriosclerotic disease in humans," it apparently means that the specification does not reasonably provide enablement for determining *every* arteriosclerotic disease in humans – because myocardial infarction is an arteriosclerotic disease and the Office has stated that the specification enables a method of determining myocardial infarction. Thus, the question is whether the specification – given that the Office accepts that determining myocardial infarction is enabled – enables determination of *other* diseases (beyond myocardial infarction) within the scope of arteriosclerotic diseases. Applicants submit that it does.

Applicants wish to note that the specification clearly states an increased risk of *arteriosclerotic disease* can be determined in humans by detecting a C/A polymorphism at nucleotide 80 in the nucleotide sequence of exon 3 of the LT-α gene shown in SEQ ID NO: 3. It is well accepted that a specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Thus, the initial burden is on the Office to come forward with evidence to show that the claim is not enabled by the specification.

In the present Office Action, the Office's evidence to support its lack-of-enablement arguments is Asselbergs et al. (Clinical Science, (2007), Vol. 112, pages 291-298, hereinafter "Asselbergs"), a newly cited post-filing document. The Action states that Asselbergs teaches that with regard to coronary heart disease and the detection of the SNP there was no association (Office Action, page 8, first full paragraph, citing to the Abstract of Asselbergs). The Action concludes that coronary heart disease is a type of arteriosclerosis heart disease and as such, Asselbergs teaches there is no association between the claimed SNP and a particular type of arteriosclerotic disease. Thus, the Office's position is that because Asselbergs allegedly showed that a type of arteriosclerotic disease, i.e., coronary heart disease, is not associated with the claimed SNP, that the claims must therefore not be enabled for their full scope. Applicants respectfully disagree with this conclusion.

Applicants first wish to point out that Asselbergs does not define "coronary heart disease." However, from the "Methods" section (right column of page 292), it appears that the specific disease that was studied was actually myocardial infarction. Note, for example, the results shown in Table 1 (page 293), which summarizes results for "women and men who developed non-fatal myocardial infarction or fatal [coronary heart disease]." Additionally, the study population described in the right column of page 292 suggests that the authors were interested in those persons who had non-fatal myocardial infarction or fatal coronary heart disease. While the authors do not state what the direct cause of death was in the fatal coronary heart disease patients, it is reasonable to assume that it was a fatal myocardial infarction. Thus, what Asselbergs apparently shows is that there is *no* association with myocardial infarction – which is exactly the opposite of Applicants' findings, not to mention entirely inconsistent with the Office's admission regarding enabled subject matter.

Applicants submit that there are reasons to explain why Asselbergs' findings are inconsistent with the present invention. As shown in The PROCARDIS Study (European Journal of Human Genetics (2004), pages 770-774), which Applicants provided with the previous response, the association of LTA Thr26Asp with coronary artery disease was demonstrated using a linkage disequilibrium test (wherein the hierarchization of a group can be ignored) based on a European large scale family of coronary artery disease (ischemic cardiac disease). Although Asselbergs discloses case-control association analysis using samples of American peoples, it is very possible that exact results cannot be obtained in this method when a hierarchization sample is used. It is widely recognized that the Japanese peoples are an almost homogeneous population, but hierarchization of the group exists for Caucasian peoples. Additionally, the number in the samples used in Asselbergs was small, and an insufficient sample size for detecting a disease association.

Applicants note that the aforementioned PROCARDIS Study states that there is a "strongly reinforce[d] . . . contention that [the LTA 252G/N26] haplotype, defined by at least three functional SNPs, may be causally related to MI [myocardial infarction] and/or CAD [coronary artery disease]." (Page 773). The PROCARDIS Study goes further to say that its results, "together with the Japanese case:control study, suggested that it is the 252G/N26-containing haplotype that is important *in vivo* in the MI/CAD association." (Page 772).

Applicants note that the PROCARDIS study utilized linkage-disequilibrium (LD) test analyses. (Page 770).

Applicants also respectfully note that Asselbergs also fails to rebut the findings of The PROCARDIS Study. Applicants note that Asselbergs states that several studies have examined the association between LTA gene polymorphisms and coronary heart disease, but Asselbergs only states that these studies were based on identification of prevalent cases and were inconsistent. (See page 292, column 1). There is nothing in Asselbergs that indicates why any of these cases would be flawed or incorrect, or why the results of The PROCARDIS Study (which support the present invention) are somehow incorrect.

On the other hand, Applicants submit that The PROCARDIS Study rebuts the findings of Asselbergs. In The PROCARDIS Study, which used a heterogeneous European population in the study, and utilized the LD test, an association between the LTA SNP and coronary artery disease and/or myocardial infarction was found. Applicants note that when the appropriate types of tests are used (e.g., linkage-disequilibrium tests), on the appropriate sample groups, the association of the LTA SNP and arteriosclerotic disease is observed.

Applicants further note that the Office has not provided any reason that The PROCARDIS Study, which Applicants have provided in support of the enablement, is flawed or incorrect. Indeed, to the extent that the Office comments on The PROCARDIS Study, it notes that Applicants' arguments were persuasive. (Office Action, page 12.)

In summary, Applicants note that the specification clearly demonstrates that an increased risk of arteriosclerotic disease can be determined in humans by detecting a C/A polymorphism at nucleotide 80 in the nucleotide sequence of exon 3 of the LT-α gene shown in SEQ ID NO: 3. This finding is consistent with The PROCARDIS Study, which demonstrated the same correlation in a large European population, and followed studies of Japanese populations that had observed the same correlation. The Office relies upon a post-filing publication to show that other arteriosclerotic diseases are not associated with the claimed SNP, but as Applicants have explained herein, that publication actually relates to myocardial infarction and its directly contradictory results are explained away by its apparently limited sample population and failure

to make adequate statistical controls. Thus, Applicants respectfully submit that the Office's newly cited publication is insufficient to rebut the strong enablement showing of the present specification, combined with other post-filing art.

In view of the foregoing remarks and amendments, Applicants respectfully submit that the claimed invention is enabled, and respectfully request withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

CONCLUSION

In view of the foregoing, the Examiner is respectfully requested to withdraw the rejections of record and allow all the pending claims. Applicants invite the Examiner to contact the undersigned with any questions.

Respectfully Submitted,
Toshihiro TANAKA et al.

Bruce H. Bernstein
Reg. No. 29,027 42,920

August 26, 2009
GREENBLUM & BERNSTEIN, P.L.C.
1950 Roland Clarke Place
Reston, VA 20191
(703) 716-1191